DESCRIPTION

ANGIOGENESIS INHIBITOR

Technical Field

[0001]

The present invention relates to an angiogenesis inhibitor. Specifically, the present invention relates to a prophylactic or therapeutic agent against a disease or condition in which angiogenesis is involved, such as, for example, proliferation, recurrence, or metastasis of malignant solid tumor, corneal angiogenesis, pterygium, conjunctivitis, rubeosis iridis, neovascular glaucoma, proliferative retinopathy, central retinal vein occlusion, diabetic retinopathy, retinal angiogenesis, or age-related macular degeneration.

Background Art

[0002]

Angiogenesis refers to a phenomenon that new vessels are formed from existing vessels, and is known to be physiologically essential e.g. for wound healing and placentation during pregnancy. Meanwhile, angiogenesis has been also indicated to be responsible for the formation of a disease or pathological condition (Carmeliet P., Nature Med., 9(6), 653-660 (2003)). In addition to proliferation, recurrence, or metastasis of malignant solid tumor, a disease or condition particularly known in ophthalmologic field, such

as corneal angiogenesis, pterygium, conjunctivitis, rubeosis iridis, neovascular glaucoma, proliferative retinopathy, central retinal vein occlusion, diabetic retinopathy, retinal angiogenesis, or age-related macular degeneration is known as a disease or pathological condition mentioned above. (Chang JH, Gabison EE, Kato T, Azar DT, Curr. Opin. Ophthalmol., 12(4), 242-249 (2001)).

As a mechanism of angiogenesis, a process is known from the activation of vascular endothelial cells by factors such as VEGF (vascular endothelial growth factor) and FGF (fibroblast growth factor)-2 to the digestion of vascular basement membranes by proteases such as matrix metalloprotease and urokinase, and to the subsequent proliferation/migration and redifferentiation (luminal formation and basement membrane regeneration) of the cells and the reconstruction of vascular walls by perithelial cells.

[0003]

In view of such a background, attention has been given in recent years to development of a therapeutic agent using angiogenesis inhibition as a mechanism, and studies of angiogenesis inhibitors based on various action mechanisms including inhibited VEGF function have been widely carried out (Chang JH, Gabison EE, Kato T, Azar DT, Curr. Opin. Ophthalmol., 12(4), 242-249 (2001) and Dredge K, Dalgleish AG, Marriott JB, Curr. Opin. Investig. Drugs, 4(6), 667-674 (2003)). However, it is yet hard to say that sufficient outcomes have been achieved, and there is need for development of a new agent having an angiogenesis-inhibiting effect.

Disclosure of the Invention

[0004]

Thus, an object of the present invention is to provide a novel angiogenesis inhibitor, and a prophylactic or therapeutic agent, using the same, against a disease or condition in which angiogenesis is involved, for example, proliferation, recurrence, or metastasis of malignant solid tumor, corneal angiogenesis, pterygium, conjunctivitis, rubeosis iridis, neovascular glaucoma, proliferative retinopathy, central retinal vein occlusion, diabetic retinopathy, retinal angiogenesis, or age-related macular degeneration.

[0005]

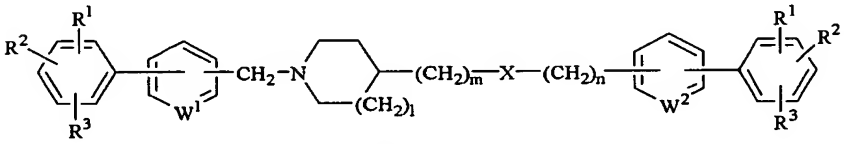
In view of the current condition, as the result of searching for substances having an effect on angiogenesis using cultured cell lines, the present inventors have found that compounds represented by the general formula (1) to be described have, very surprisingly, an excellent angiogenesis-inhibiting effect and are useful as a prophylactic or therapeutic agent against proliferation, recurrence, or metastasis of malignant solid tumor, corneal angiogenesis, pterygium, conjunctivitis, rubeosis iridis, neovascular glaucoma, proliferative retinopathy, central retinal vein occlusion, diabetic retinopathy, retinal angiogenesis, age-related macular degeneration, and the like, thereby accomplishing the present invention.

[0006]

Thus, the present invention provides a method for treating a disease or condition caused by angiogenesis, comprising administering an effective amount of a cyclic amine compound represented by the general formula (1), a salt or a solvate thereof:

[0007]

[Formula 1]



(1)

[0008]

wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen-substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1.

The present invention also provides a method for inhibiting angiogenesis, comprising administering an effective amount of a cyclic amine compound represented by the formula (1) above, or a salt thereof, or a solvate thereof to patients in need thereof.

[0009]

The present invention further provides an angiogenesis inhibitor comprising, as an active ingredient, a cyclic amine compound represented by the formula (1) above, or a salt thereof, or a solvate thereof.

The present invention further provides a prophylactic or therapeutic agent against a disease or condition caused by angiogenesis, comprising, as an active ingredient, a cyclic amine compound represented by the formula (1) above, or a salt thereof, or a solvate thereof.

[0010]

The present invention further provides use of a cyclic amine compound represented by the formula (1) above, or a salt thereof, or a solvate thereof for producing an angiogenesis inhibitor.

The present invention further provides use of a cyclic amine compound represented by the formula (1) above, or a salt thereof, or a solvate thereof for producing a prophylactic or therapeutic agent against a disease or condition caused by angiogenesis.

[0011]

According to the present invention, a novel angiogenesis inhibitor can be provided, and a prophylactic or therapeutic agent can be further provided against a disease or condition in which angiogenesis is involved, such as proliferation, recurrence, or metastasis of malignant solid tumor, corneal angiogenesis, pterygium, conjunctivitis, rubeosis iridis, neovascular glaucoma, proliferative retinopathy, central

retinal vein occlusion, diabetic retinopathy, retinal angiogenesis, or age-related macular degeneration.

Brief Description of the Drawings

[0012]

Figure 1 is a picture showing the condition of angiogenesis when each of the compounds was added; and

Figure 2 is a pair of graphs showing effects of each of the compounds on tubule area (A) and tubule length (B).

Best Mode for Carrying Out the Invention

[0013]

The compounds represented by the general formula (1) used in the present invention have an excellent cell adhesion-inhibiting effect as described in WO03/02703, which discloses the application thereof to allergic disease, autoimmune disease, and chronic inflammatory disease, but it is undisclosed whether they have an angiogenesis-inhibiting effect or not. The content of WO03/02703 including a process for producing compounds of the general formula (1) and a method for preparing formulations containing compounds of the general formula (1) is herein incorporated by reference.

[0014]

In the formula (1), halogen atoms represented by R^1 to R^3 include a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom.

[0015]

Alkyl groups represented by R^1 to R^4 include C_1-C_8 linear, branched, or cyclic alkyl groups; the C_1-C_8 linear or branched alkyl groups include, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl, and the C_3-C_8 cyclic alkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, and cyclohexylethyl. Among these, C_1-C_6 alkyl groups such as methyl, ethyl, n-propyl, isopropyl, and n-butyl are particularly preferable.

[0016]

Halogen-substituted alkyl groups represented by R^1 to R^3 include C_1-C_8 alkyl groups each substituted by 1 to 3 halogen atoms; among these, C_1-C_6 alkyl groups each substituted by 1 to 3 halogen atoms, such as trifluoromethyl and 2,2,2-trifluoroethyl are particularly preferable.

[0017]

Alkoxy groups include C_1-C_8 linear, branched, or cyclic alkoxy groups; the C_1-C_8 linear or branched alkoxy groups include, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, and hexyloxy, and the C_3-C_8 cycloalkyloxy groups include, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cyclohexylmethyloxy, and cyclohexylethyloxy. Among these, C_1-C_6 alkoxy groups such as methoxy, ethoxy, n-propoxy, isopropoxy, and n-butoxy are particularly preferable.

[0018]

Alkylthio groups include C_1-C_8 alkylthio groups; for example, C_1-C_6 alkylthio groups such as methylthio, ethylthio, n-propylthio, and isopropylthio are preferable.

[0019]

Alkoxycarbonyl groups include C_1-C_6 alkoxycarbonyl groups; for example, C_1-C_4 alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl are preferable.

[0020]

Alkanoyl groups include C_1-C_6 alkanoyl groups; for example, C_1-C_4 alkanoyl groups such as acetyl, propionyl, butylyl, and isobutylyl are preferable.

[0021]

Alkenyl groups represented by R^4 include C_3-C_8 alkenyl groups; for example, C_3-C_6 alkenyl groups such as 2-propenyl, and 3-butenyl are preferable. Alkynyl groups include C_3-C_8 alkynyl groups; for example, C_3-C_6 alkynyl groups such as 2-propynyl and 3-butynyl are preferable.

[0022]

Aryl groups represented by R^4 include C_6-C_{14} aryl groups; for example, phenyl, naphtyl, anthryl, indenyl, indanyl, and 5,6,7,8-tetrahydronaphthyl are preferable.

[0023]

Heteroaryl groups represented by R^4 include 5- or 6-membered heteroaryl groups containing 1 to 4 nitrogen atoms; for example, imidazolyl, pyridyl, and pyrimidinyl are preferable. Aralkyl groups represented by R^4 include C_6-C_{14} aryl-C_1-C_6 alkyl groups, including, for example, phenyl-C_1-C_6

alkyl or naphtyl-C_1-C_6 alkyl groups such as benzyl, naphtylmethyl, phenylethyl, and phenylpropyl. Heteroaralkyl groups represented by R^4 include 5- or 6-membered heteroaryl-C_1-C_6 alkyl group containing 1 to 4 nitrogen atoms, including, for example, imidazolyl-C_1-C_6 alkyl groups, pyridyl-C_1-C_6 alkyl groups, and pyrimidinyl-C_1-C_6 alkyl groups.

[0024]

Groups with which these aryl, heteroaryl, aralkyl, or heteroaralkyl groups can be substituted may be 1 to 3 groups or atoms selected from an alkyl group, an alkoxy group, a halogen-substituted alkoxy group, an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group. Here, alkyl, alkoxy and alkylthio groups include the same as those described in the above R^1 to R^3. The alkyl groups of alkylsulfinyl and alkylsulfonyl groups include C_1-C_3 alkyl groups, particularly methyl, ethyl, n-propyl, and isopropyl. The halogen-substituted alkoxy group is preferably a C_1-C_8 alkoxy group substituted by 1 to 3 halogen atoms, particularly a C_1-C_4 alkoxy group substituted by 1 to 3 halogen atoms, including trifluoromethoxy or 2,2,2-trifluoroethoxy. Alkylenedioxy groups include C_1-C_3 alkylenedioxy groups such as methylenedioxy, ethylenedioxy, and propylenedioxy.

[0025]

X is preferably NR^4 where R^4 is preferably a C_1-C_8 alkyl group, a substituted or unsubstituted C_6-C_{14} aryl group, a

substituted or unsubstituted 5- or 6-membered heteroaryl group containing 1 to 4 nitrogen atoms, a substituted or unsubstituted C_6-C_{14} aryl-C_1-C_6 alkyl group, or a C_1-C_6 alkyl group having a substituted or unsubstituted 5- or 6-membered heteroaryl group containing 1 to 4 nitrogen atoms.

[0026]

Preferably, R^1, R^2 and R^3 bond to the 3-, 4-, and 5-positions of the phenyl group, respectively. Here, it is particularly preferred that R^1 and R^3 (that is, the 3- and 5-positions on the phenyl group) are an alkoxy group or a halogen atom. R^2 (that is, the 4-position on the phenyl group) is preferably a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen-substituted alkyl group, an alkoxy group, an alkylthio group, a carboxy group, an alkoxycarbonyl group, or an alkanoyl group.

[0027]

Although l represents 0 or 1, 1 is preferable.

W^1 is preferably N. W^2 is also preferably N.

[0028]

Among the compounds of formula (1), those where X is NR^4 and R^4 is a C_1-C_8 alkyl group, a substituted or unsubstituted C_6-C_{14} aryl group, a substituted or unsubstituted 5- or 6-membered heteroaryl group containing 1 to 4 nitrogen atoms, a substituted or unsubstituted C_6-C_{14} aryl-C_1-C_6 alkyl group, or a C_1-C_6 alkyl group having a substituted or unsubstituted 5- or 6-membered heteroaryl group containing 1 to 4 nitrogen atoms are preferable. Further, it is particularly preferable that R^4 is a phenyl or pyridyl group optionally substituted

by one or two groups or atoms selected from a halogen atom, an alkyl group, an alkoxy group, an alkylthio group, a trifluoromethyl group, and an alkylenedioxy group. Alternatively, a C_1-C_8 alkyl group is particularly preferable.

[0029]

More specifically,

4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine,

4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine, or a salt thereof is most preferable.

[0030]

Salts of the above compound (1) are not particularly restricted in so far as they are pharmaceutically acceptable salts, but can include, for example, mineral acid addition salts such as hydrochloride, hydrobromate, hydroiodide, sulfate, and phosphate; and organic acid addition salts such as benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, oxalate, maleate, fumarate, tartrate, citrate, and acetate.

[0031]

In addition, the above-described compound (1) can be present in the form of a solvate typified by a hydrate, and the solvate is also intended to be embraced in the present invention.

[0032]

The compound (1) has an effect of potently inhibiting angiogenesis as shown in Example to be described, and is useful as a prophylactic or therapeutic agent against a disease or pathological condition caused by angiogenesis in mammals including human, such as, for example, proliferation, recurrence, or metastasis of malignant solid tumor, corneal angiogenesis, pterygium, conjunctivitis, rubeosis iridis, neovascular glaucoma, proliferative retinopathy, central retinal vein occlusion, diabetic retinopathy, retinal angiogenesis, or age-related macular degeneration.

[0033]

The medicine according to the present invention contains the above-described compound (1), a salt thereof, or a solvate thereof as an active ingredient, and the mode of administration is not particularly restricted and may be properly selected depending on the therapeutic purpose; examples thereof include oral administration using tablets, capsules, granules, powders, syrups, or the like and parenteral administration using intravascular injections, intramuscular injections, suppositories, ointments, inhalants, eye drops, nasal drops, patches or the like. Compositions suitable for these modes of administration are formulated with pharmaceutically acceptable carriers, and may be produced by a conventional preparation method well known to those skilled in the art. The carrier may use the proper combination of excipient, binder, extender, disintegrator, surfactant, lubricant, dispersant, buffer, preservative, coloring agent, flavor, smell

correcting agent, perfume, film forming agent, diluent, and the like.

[0034]

The dosage of the medicine according to the present invention varies depending on the age, sex, body weight, and symptoms, the mode and frequency of administration, and the like; however, it is preferable that the medicine is usually administered orally or parenterally at a daily dose of 0.01 to 1000 mg, preferably 0.1 to 100 mg in the above-described compound (1) once or in several divided portions.

Examples

[0035]

The present invention is further specifically described below, based on Examples. However, the scope of the present invention is not intended to be limited by these Examples.

[0036]

Synthesis Example 1

Synthesis of 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine citrate

The synthesis was carried out according to Example 13 (4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride) described in WO03/02703, followed by converting the resultant free base to the citrate thereof to provide the title compound in the form of white to pale yellow powder.

[0037]

Decomposition point: 126 to 129°C

NMR: (400MHz, DMSO-d_6) δ: 1.66 to 1.75 (m, 2H), 1.84 (d, 2H, J=10.7 Hz), 2.30 (t, 2H, J=11.5 Hz), 2.68 (dd, 4H, J=3.7 Hz, 15.4 Hz), 2.98 (d, 2H, J=11.2 Hz), 3.50 to 3.55 (m, 1H), 3.64 (s, 3H), 3.69 (s, 2H), 3,71 (s, 3H), 3.73 (s, 3H), 3.84 (s, 6H), 3.86 (s, 6H), 4.46 (s, 2H), 6.76 (d, 2H, J=9.0 Hz), 6.85 (s, 2H), 6.86 (d, 2H, J=8.8 Hz), 7.83 (d, 1H, J=4.9 Hz), 7,35 (s, 2H), 7.83 (s, 2H), 8.42 (s, 1H), 8.57 (d, 1H, J=4.9 Hz), 8.68 (d, 1 H, J=2.2 Hz)

[0038]

Example 1: Examination of an angiogenesis-inhibiting effect using cultured cells

As an in vitro angiogenesis model, a model for evaluating tubule formation induced by coculturing vascular endothelial cells and fibroblast has been reported (Bishop ET, Bell GT, Bloor S, Broom IJ, Hendry NFK, Wheatley DN, Angiogenesis, 3, 335-344 (1999)). This system was used to examine the effects of compounds on angiogenesis.

[0039]

1) Compounds used

In addition to the compound obtained in Synthesis Example 1 above (hereinafter denoted as compound 1), a compound described in Example 10 of WO03/02703, i.e., 4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride (hereinafter

referred to as compound 2) synthesized according to the described method was used for the following examination.

[0040]

2) Preparation of compound solutions

Compound 1 and 2 were each dissolved in dimethylsulfoxide (DMSO) to prepare 3, 1, 0.3, and 0.1 mmol/L of compound solutions. Each of the DMSO solutions of the compounds (1 and 2) with the concentrations (0.1 to 3 mmol/L) prepared, or DMSO (for a compound-free group) was diluted 1,000 times using a medium dedicated to angiogenesis (from Kurabo Industries Ltd.) containing 10 ng/mL VEGF-A (from Kurabo Industries Ltd.), to prepare 0 (compound-free group), 0.1, 0.3, 1, or 3 μmol/L of a solution of each of the compounds (1 and 2). The medium dedicated to angiogenesis containing DMSO, to which VEGF-A was not added, was also prepared as a negative control.

[0041]

3) Examination of an angiogenesis-inhibiting effect of the compounds

A. Test method

The angiogenesis-inhibiting effects of the compounds were evaluated using "Angiogenesis Kit" from Kurabo Industries Ltd. according to the procedure described in the protocol thereof. After obtaining the cells, the cell culture medium was exchanged every 2 to 3 days, and immunostaining was performed using an anti-CD 31 antibody on the 11th day of culture to observe and photograph the microvessel-like structure formed under a microscope. The resultant image data was analyzed using an image processing/quantitation software

(from Kurabo Industries Ltd.) to determine the activity of inhibiting angiogenesis.

[0042]

B. Results

Microscopic images by which the effects of the compounds on angiogenesis were evaluated are shown in Figure 1. Figure 2 is a pair of graphs showing the tubule area (A) and tubule length (B) quantified on the basis of each image data. Five visual fields for each group were photographed and quantified to calculate the mean ± standard error. As shown in Figures 1 and 2, it was demonstrated that compounds 1 and 2 inhibited angiogenesis at concentrations of 0.3 μmol/L or more.